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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,540	03/08/2001	Adrian Bot	A30571-A-PCT/USA-A	7183

7590 10/01/2009

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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
10/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/801,540	BOT ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/12/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2 are pending and under consideration. Claim 3 is canceled.

Applicant's arguments filed 4/3/09 have been fully considered.

Applicant's submission of exhibits A-C on 4/3/09 has been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Claims 1-2 under 35 U.S.C. 103(a) as being unpatentable over Meheus et al, [postgraduate Medical Journal, 63(Supp 2): 139-141, 1987 (IDS)] in view of Whalen et al, (Ann NY Acad Sci, 772:64-76, 1995); Schirmbeck et al, (Journal of Virology, 69(10): 5929-5934, 1995) is maintained for the reasons of record in the office action mailed on 1/7/09.

A. Applicants argue as conceded by the Examiner, Meheus does not teach a method comprising inoculating an infant human with a naked nucleic acid encoding an epitope within the age of birth to one month.

In response these arguments are not persuasive because the examiner specifically stated: "Meheus et al, differ from the present invention for not teaching a naked recombinant nucleic acid encoding a relevant epitope to the target HBsAg" (see office action mailed on 1/7/09, page 3, 2nd paragraph, last sentence). Meheus is not cited for a nucleic acid encoding a relevant epitope vaccine but Meheus is cited for his teachings of infants vaccinated with a

recombinant DNA vaccine within the time limit as instantly claimed that is within 24 hours after birth according to a 0, 1, 2, month schedule (see same paragraph of office action). Thus, Meheus is cited for the time limit within the age of birth to one month as instantly claimed (emphasis added). Meheus teaches infants vaccinated with recombinant DNA [10 micrograms (protein)] vaccine within the first month after birth and not a nucleic acid encoding an epitope vaccine. The nucleic acid encoding an epitope vaccine deficiency is cured by the combined references of Whalen and Schirmbeck (see pages 3-5).

Second Applicants argue in Meheus, infants born to HBsAg-positive mothers (Group I) and infants born to women without HBV markers (Group II) were vaccinated with a protein vaccine within 24 hours after birth according to a 0, 1, and 2 month schedule, with a booster dose planned 12 months later, and the immunogenicity of the vaccine was evaluated based on the seroconversion rates measured in sera collected from the newborns (abstract). The seroconversion rate for Group I increased from 40% at Month 1 to 86% at Month 4 (Table I) while the seroconversion rate for Group II increased from 46% at Month 1 to 100% at Month 4 (Table II). Applicant's ague that the experimental design and results reported in Meheus are consistent with the then conventional view of infant tolerance and the general knowledge that human neonates start to synthesize their own antibodies at about 3-4 months after birth.

In response these arguments are not persuasive because neither the disclosed teachings in the specification nor any evidence provided by Applicants provide guidance for lack of immunogenicity to the recombinant DNA hepatitis B vaccine as taught by Meheus in the infants after birth within the first month because of seroconversion. In fact, Meheus teaches that recombinant protein is safe and highly immunogenic in newborns and no adverse effects were seen and vaccination results in neonates showed even at two months after third dose of vaccine. **Meheus** teaches infants of HBsAg-positive mothers (Group I) as well as those born to

women without HBV markers (Group II) were vaccinated with recombinant protein hepatitis B vaccine within 24 hours after birth according to a 0, 1, and 2 month schedule, with a booster dose planned 12 months later (abstract). Vaccination results in 14 (Group I) and 47 (Group II) neonates showed that at two months after the third dose of vaccine, 86% (6/7) and 100% (37/37), respectively, seroconverted, with anti-HBs geometric mean titers of 80 IU/l and 266 IU/l in the respective groups, therefore there is no lack of immunogenicity even after follow up at two months. Thus, in contrast to Applicant's arguments Meheus teaches the vaccine is highly immunogenic and the follow up data after the third dose of vaccine there is sustained immunogenicity and there is no evidence of Meheus teaching infant tolerance and/or human neonates start to synthesize their own antibodies at about 3-4 months after birth.

Third, Applicants argue Meheus does not teach whether and/or to what extent an epitope encoded by a nucleic acid would be expressed and capable of inducing immune responses in an infant human after being inoculated with the naked nucleic acid within the age of birth to one month. One of ordinary skill in the art would have expected a lower amount of the expressed epitope and, therefore, a lower seroconversion rate in an infant human inoculated with a naked nucleic acid encoding the epitope than an infant human inoculated with the epitope. Thus, one of ordinary skill in the art would not have been motivated to modify the protein vaccination method disclosed in Meheus by inoculating an infant human with a naked nucleic acid within the age of birth to one month with a reasonable expectation of success in inducing immune responses in the infant human.

These argument are not persuasive because first Meheus as discussed is not cited for teachings a nucleic acid encoding an epitope vaccine thus accordingly is not expected to teach to any extent inducing an immune response via said vaccine but Meheus is used for his teachings of a protein vaccine within the first month of a human infant specifically within the time

limit of one month after birth of a human neonate, as instantly claimed. Second, Applicants have failed to provide guidance as to why a skilled artisan would have expected a lower amount of the expressed epitope and therefore a lower seroconversion rate in a nucleic acid encoding vaccine rather than a protein vaccine and how this is related to the teachings of Meheus of a recombinant vaccine within the first month of a human infant for which Meheus is cited for in the instant rejection.

B. First, Applicants argue that Whalen and Schirmbeck do not teach inoculation of an infant human within the age of birth to one month or a non-human infant of an equivalent age. Neither Whalen nor Schirrnbeck teaches a method comprising inoculating an infant human with a naked nucleic acid within the age of birth to one month or a non-human infant of an equivalent age.

In response this is not persuasive because Whalen and Shirmbeck are cited for the development of plasmid-mediated immunization to hepatitis B surface antigens and the activation of the immune response and not for the one month old human infant as Applicants argue. In fact, Whalen teaches based on the 15 year experience with the recombinant HBV (protein) vaccine protection from HBV infection is essential and yet immunization is often unsuccessful because of low humoral immune response in mice which mimics the low humoral immune response in humans and the mouse model is the appropriate model for HBV DNA-mediated immunization (p 65, 2nd to 3rd paragraph). Whale teaches data concerning DNA-based immunization and the response to HBsAg in particular and proposes explanations for the mechanism and efficacy of HBV DNA-based immunization (p 66-73). Therefore, Whalen provides motivation to replace protein HBV vaccination with DNA-based immunization.

Second, Applicants argue that Whalen on page 68 cites three references by incorporation that is references 4-6 which Applicants submitted as Exhibit A-C respectively.

Applicants argue that said references teach in vivo gene transfer to mice of approximately 6-7 weeks old (Davis 1994, p. 1505; Davis 1993, p. 1851) while Michel teaches in vivo gene transfer to 6- to 8-week-old mice (Michel, p. 5308).

In response these argument because as discussed above Whalen is not cited for the age of the in vivo gene transfer but Whalen is cited for his teachings of HBV DNA-based immunization and Whalen provides the motivation to replace the HBV protein vaccine with the DNA-based vaccine based on the low response of the protein HBV vaccine and the induction of a humoral and cellular response to HBsAg following DNA-based immunization. Specifically, on page 68 cited by Applicants Whalen teaches intramuscular injection of plasmids carrying the HBsAg determinants in mice induce antibodies to the HBsAg and refers to the exhibits A-C submitted by Applicants. Whalen in the same paragraph teaches and refers to exhibit C submitted by the Applicants (incorporation by reference by Whalen) that the DNA-based immunization to the hepatitis B surface antigen in mice and aspects of the humoral response mimics hepatitis B viral infection in humans (see exhibit C, Title). In exhibit C Michel et al compares the specificity of the humoral immune response obtained after DNA-mediated immunization using several plasmid vectors encoding the different HBV envelope proteins and also teaches the humoral immune response induced by in situ production of the protein antigens in mice mimic aspects of that which occur during natural infection in humans. Thus, Whalen provides sufficient motivation to replace HBV protein-mediated immunization with DNA-based immunization and in contrast to Applicant's assertions Whalen is not cited for the age of the immunized human infants but Meheus is cited for the age of the age of the human infant. Whalen teaches the extent of seroconversion after immunization with protein HBV vaccine is high in health young adults (not in one month old infants as instantly claimed); however, increasing age can diminish the response to the vaccine (see Whalen p 65, 2nd paragraph).

Thus, the combined teachings of Meheus and Whalen provide sufficient motivation to replace HBV protein-mediated immunization with HBV DNA-mediated immunization in one month old human infants.

Third, Applicants argue that Schirmbeck teaches inoculating mice at 12 to 16 weeks of age (p. 5930). While a human infant ranges from birth to about nine months, a mouse infant ranges from birth to about four weeks of age (specification, page 13, line 30 to page 14, line 1). Thus, Whalen, Davis 1994, Davis 1993, Michel and Schirmbeck teach inoculating adult mice, not mice of an age equivalent to an infant human within the age of birth to one month. Accordingly, Whalen and Schirmbeck do not teach or suggest inoculating a human infant at an age ranging from birth to one month for immunization or for inducing a cytotoxic T cell response, and one of ordinary skill in the art would not have been motivated by Whalen and Schirmbeck to apply the plasmid DNA HBsAg epitope vaccine of Schirmbeck in neonates of Meheus, or to inoculate an infant human with a naked nucleic acid encoding HBsAg within the age of birth to one month with a reasonable expectation of success in immunizing or inducing cytotoxic T cell response against HBsAg in the one month old human infant.

Again as discussed above Meheus and not Whalen or Schirmbeck is cited for the one month old human infant but Meheus teaches the HBsAg immunization for a one month old human infant.

C. Applicants argue a combination of Meheus, Whalen and Schirmbeck does not teach each and every element of claim 1 or 2. These references do not teach or suggest inoculating an infant human with a naked nucleic acid within the age of birth to one month. It was unpredictable whether and/or to what extent an epitope encoded by a nucleic acid would be expressed and capable of immunizing or inducing a cytotoxic T cell response in an infant human inoculated with the naked nucleic acid within the age of birth to one month. For the foregoing

reasons, one skilled in the art would not have been motivated to combine Meheus, Whalen and Schirmbeck with a reasonable expectation of success in achieving the claimed invention of claim 1 or 2.

In response this if not persuasive because the combined teachings of Meheus, Whalen and Schirmbeck provide the elements of DNA -based immunization of an infant human against HBV target antigen, by a plasmid encoding one or more HBV relevant epitope antigens as taught by plasmid vectors induces strong CTL responses as well as a dominant Th1 phenotype and Schirmbeck provide the elements of DNA -based immunization by intramuscular transfer of plasmid DNA encoding HBsAg epitopes under appropriate promoter control the most potent priming of class I-Whalen DNA-mediated immunization with the HBsAg-expressing restricted CTL to HBsAg in vivo and to be used successfully with the Ld-restricted S28-39 epitope a CTL epitope of HBsAg detectable in *H-2d* BALB/c mice. Meheus provides the teachings for replacing HBV protein immunization due to the low humoral response in one month old human infants while the combined references of Whalen and Schirmbeck provide the elements of DNA -based immunization against HBV as discussed above. Thus the rejection is maintained and the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305. The examiner can normally be reached on Monday through Friday from 9 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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